HYPOTHYROIDISM DIAGNOSIS AND TREATMENT*

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THE term hypothyroidism obviously signifies a state in which the individual receives less of the hormone characteristic of the thyroid than is required by his body economy for the preservation of health. We are all quite familiar with such clinical varieties of hypothyroidism as cretinism, endemic or sporadic, and the myxedema of children and of adults. We also recognize hypothyroidism following extensive surgical removal of thyroid tissue, or destruction of thyroid tissue by certain types of chronic inflammation.

I have been asked to discuss with you the diagnosis and treatment of these conditions and that I will do: but I must say something also of etiology and morbid physiology because it is upon these that sound clinical practice must rest.

Adult myxedema was first described by Gull in 1874 and its cure by the administration of thyroid was contributed by Murray in 1891. It is of interest to note that Murray died September 23, last—the father of endocrine-substitution therapy. It is also worth noting that probably the first patient to receive his treatment in the United States is still alive at the age of eighty-seven. Mrs. B. is now the patient of Alexander Burgess, of Providence, who kindly gives me frequent bulletins of her progress. Her symptoms were first noted in 1888 and her doctor diagnosed Bright's disease and said she could not live six months. In 1892 another doctor, keener in diagnosis and up to date on his literature, diagnosed myxedema and started her on thyroid. She has taken it ever since.

The case of Mrs. B. teaches us the calamity of missing the diagnosis of myxedema. Had it not been made she would have died in 1903 or earlier, because fifteen years seems to be as long as one can live after the onset of myxedema without thyroid therapy. The symptoms and signs of myxedema are so striking, so characteristic, that there would seldom seem

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to be any excuse for missing the diagnosis. The classic picture should be familiar to every doctor, and if when present there can likewise be demonstrated low basal metabolic rate—minus thirty-five or lower—and elevated blood cholesterol, the diagnosis is practically certain. Nevertheless, in our clinic we get patients each year in whose cases the diagnosis has been missed. Often the error is in supposing that the patient has Bright's disease. Doctors thus give us the opportunity to make cures which they could easily have made themselves, and for which they could have got the credit.

A few years ago I would have told you that spontaneous, acquired myxedema of adults is due to primary atrophy of the thyroid; that the effect of this atrophy is to produce a simple athyreosis, the effects of which can be completely corrected by the administration of sufficient quantities of dried thyroid gland. The only reservation I would have made would have been that in patients with arteriosclerosis you must beware of producing angina pectoris by too rapid elevation of the rate of metabolism, with a resulting inadequacy of coronary blood flow.

Today these statements will still hold in most instances, but recent experience has indicated that there are a few cases of what clinically is myxedema in which the etiology is different and the indications for treatment different. These are cases in which the primary fault lies in the pituitary instead of in the thyroid. The myxedema is the result of a hypothyroidism due to lack of stimulation of the thyroid by the pituitary, rather than to primary failure of the thyroid itself. Actually these patients have a form of pituitary cachexia, or Simmonds' disease, but for reasons unknown, the emphasis in their symptomatology is so strikingly on their hypothyroid manifestations that other hypopituitary symptoms or signs escape attention in the clinical evaluation.

Our attention was drawn to this special type of myxedema by the following experience. A woman of forty-eight entered December 1, 1936, with what appeared to be fairly classic myxedema of about ten years' duration. On treatment with thyroid these manifestations disappeared. However, she soon developed new symptoms—nausea, vomiting, fever, psychosis and convulsions, and died on the thirtieth day of treatment. At autopsy there was found fibrosis of the anterior lobe of the pituitary and atrophy of the thyroid, parathyroids, adrenals, ovaries and uterus. These pathologic changes are characteristic of Simmonds' disease and the terminal symptoms are like those sometimes seen in the crises of

Addison's disease.[1]

More recently, my colleague, J. Lerman, referred to the hospital a woman of thirty years (U177833), whom he thought had ordinary myxedema. On thyroid therapy she also improved as to her myxedema manifestations, but presently went into an undoubted state of adrenal insufficiency, from which, however, she was rescued by vigorous treatment with sodium chloride.

Although rare, cases of this type are important, because of the hazards of treatment with thyroid. Their detection will depend upon the discovery of evidence of coexisting underfunction of other endocrine glands than the thyroid. In women developing myxedema prior to the menopause the occurrence of amenorrhea, in place of the usual menorrhagia of myxedema, would be very suggestive of the pituitary type. However, there may be no absolute method of recognition except by very careful control of thyroid therapy in all cases of myxedema; and to the well known danger of inducing angina pectoris, we may add the occasional one of producing Addisonian crisis.

The treatment of the usual type of myxedema is so simple that we need not devote much time to it. The objective should be to rid the patient of his symptoms and clinical signs with the smallest daily ration of thyroid by mouth that will accomplish this purpose. Usually this will be found to be in the neighborhood of one to one and a half grains of thyroid U. S. P., once daily. If such dosage produces any sort of untoward symptoms, angina or other, thyroid should be stopped for a few days and then resumed in smaller dosage. We have some patients who cannot tolerate rations of over one-half to three-quarters of a grain a day. During the inauguration of thyroid therapy the doctor, for the reasons given above, should have the patient under close surveillance; and only after the size of the permanent ration has been well established, is it wise to lengthen the time between check-ups.

The treatment of the pituitary type is far from simple. Persons so afflicted are in need of all the functions of the anterior lobe of the pituitary. This might be provided either by administering the anterior lobe hormones themselves; thyrotropic, adrenotropic, gonadotropic; or the hormones which the other endocrines make under anterior lobe stimulation, namely, thyroid, cortin, estrin.

As a matter of fact, in practice good results may probably be obtained in such cases by a combination of small doses of thyroid when the

patient is protected against adrenocortical insufficiency by a high salt intake, and some preparation containing the gonadotropic principles of the anterior lobe.

The effects of hypothyroidism are more serious when the state supervenes before growth has been attained than after. The adult who acquires myxedema, if normal before the disease began, can be made normal again by adequate treatment with thyroid. On the other hand, hypothyroidism during infancy or childhood, if long untreated, will result in physical and mental stunting which no amount of substitution therapy later can altogether alleviate. Indeed, cretinous children, who have reached ten years without treatment, derive little if any benefit from thyroid. About all the effect it has upon them is to make them irritable and less manageable than when in their athyreotic vegetable-like state. The earlier in life hypothyroidism occurs, and the longer the interval before adequate treatment is established, the more grave will be the consequence.

Thus the prognosis in cretinism, that is to say, congenital hypothyroidism, whether of the endemic or sporadic variety, is problematical. Certainly the outlook is brightest when the correct diagnosis is made very early in life and treatment started and maintained throughout the growth period and thereafter. Even so, on the question, whether an absolutely normal mental development can occur, authorities differ.

The early diagnosis of cretinism depends upon recognition of the significance of characteristic facies, habitus and behavior. It can be made in the early months of infancy. Among the earliest signs, as pointed out by Talbot,[2] are a heavy expression, and pig-like appearance of the eyes. A curious yellow tint appears early on the mesial aspect of the cheeks, disappearing when the infant cries. Changes in the tone of the voice in the direction of hoarseness are always important. Later the appearance of the cretin becomes thoroughly characteristic—a round stupid face, wide flat thick nose, open drooling mouth from which protrudes an over large tongue. The neck is short and thick, the trunk short, the belly prominent, always with umbilical hernia, the skin is dry and harsh, fat pads appear about the shoulders, and dentition is delayed.

Laboratory confirmation can be had by demonstration of low basal metabolic rate, elevated blood cholesterol, or by x-ray showing delayed bone age.

As soon as the diagnosis of cretinism is made, substitution therapy with thyroid should be started, and should be continued in adequate

dosage without interruption throughout life.

The criteria of adequate dosage are several. Not only have we basal metabolic rate and blood cholesterol as measuring sticks, but also bone age, height age, and mental age. I agree heartily with Wilkins,[3] who claims that it is not sufficient to maintain basal metabolic rate and cholesterol at normal levels, but that every effort to secure the right growth rates is also essential. To make up for lost time in regard to these, Wilkins points out that it may be necessary to keep the cretin for a time mildly hyperthyroid. In my clinic the experience has been the same.

The magnitude of dosage that may achieve the desired ends is somewhat as follows:

Age	*Dosage*
2- 4 months	1/10 grain per day
4- 8 "	1/5 grain per day
8-12 "	3/10 grain per day
12-24 "	2/5 to ¾ grain per day
2- 4 years	½ to 1½ grains per day
4-12 "	1 to 3 grains per day

The reports of success with treatment vary. Certainly no amount of treatment will make the cretin more intelligent than he would have been had he not been a cretin, and in the experience of several competent observers, even with seemingly good treatment, a distressing number of cretins end up with mental ages of not over ten or eleven years, although in other respects they become quite normal adults. None the less a few do better than this; and a mental age of ten or eleven with a normal body is vastly to be preferred to the state of imbecilic dwarfism that would persist if no treatment, or inadequate or unsustained treatment, were given.

When myxedema is acquired in childhood, the child having made a normal growth in all respects up to the time hypothyroidism supervened, the results of treatment are nearly as perfect as in adult myxedema. In order to make accurate predictions of what may be expected of treatment, therefore, it is necessary to distinguish sharply in diagnosis between cretinism and juvenile myxedema. This should not be difficult because the child who has acquired myxedema does not possess the dwarfism and gross habitus of the cretin, but merely the dry skin, puffi-

ness and retardation displayed by the adult with myxedema.

In conclusion I urge you to be on the look-out for all types of hypothyroidism, for it is most unfortunate to miss the diagnosis of a curable disease. In treating adults with myxedema, be watchful for untoward effects during the inauguration of therapy, and reduce the dose of thyroid if they occur. With regard to cretins, the important points are very early diagnosis, and sustained and sufficiently large dosage of thyroid throughout life.

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